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(54) Title: TOPICAL FORMULATION FOR LOCAL DELIVERY OF A PHARMACEUTICALLY ACTIVE AGENT			
(57) Abstract			
<p>This invention relates to a composition useful in the delivery of pharmaceutically active agents through the skin. In one embodiment of the invention, the composition is formulated with a non-steroidal anti-inflammatory agent, such as ibuprofen or ketoprofen. Such formulation is rapidly absorbed through the skin to provide local relief from pain. In another embodiment of the invention, the composition is formulated with an antineoplastic agent. Such formulation is rapidly absorbed through the skin to provide local delivery to subcutaneous tumors. The composition is useful for transcutaneous delivery of other pharmaceutically-active compounds.</p>			

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DESCRIPTIONTOPICAL FORMULATION FOR LOCAL DELIVERY OF A
PHARMACEUTICALLY ACTIVE AGENT

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Background of the InventionI. Field of the Invention

This invention relates to a composition useful in the delivery of pharmaceutically active agents through the skin. In one embodiment of the invention, the composition is formulated with a non-steroidal anti-inflammatory agent, such as ibuprofen or ketoprofen; a muscle relaxant, such as cyclobenzaprine; or other active ingredient. Such formulation is rapidly absorbed through the skin to provide local relief from pain, muscle spasms, or other pathological condition. In another embodiment of the invention, the composition is formulated with an antineoplastic or other pharmaceutically-active agent. Such formulation is rapidly absorbed through the skin to provide local delivery to subcutaneous tumors and other subdermal sites in need of treatment.

II. Information Disclosure

There has been much interest in recent years in devising ways to achieve efficient transdermal delivery of pharmaceutically active agents. Dimethyl sulfoxide, DMSO, is an agent which is known to rapidly and efficiently carry dissolved agents across membranes. However, widespread use of this agent has met with considerable resistance, and its use for delivery of pharmaceutical agents is in disfavor. Other agents for achieving percutaneous delivery have been described.

Thus, in U.S. Patent No. 5,093,133, a method for percutaneous delivery of ibuprofen using a hydroalcoholic gel was described. According to that disclosure, the rate of ibuprofen absorption across the skin was highly pH dependent, dropping from about 1 mg/hour at pHs below about 5.5 to about 0.1 mg/hour at a pH of about 7.0.

U.S. Patent No. 5,210,099 described an analgesic cream which, through maintaining a pH of 4 to 7.2 such that the ibuprofen was suspended in substantially solid crystalline form, provided skin penetration at a rate of about $39.8 \mu\text{g}/\text{cm}^2/\text{hour}$. The compositions into which the ibuprofen was formulated were conventional in the art, such as the water-in-oil emulsion compositions of U.S. Patent Nos. 3,154,470; 4,385,049; and 4,794,106.

U.S. Patent No. 3,957,971 described liposomes having (i) a matrix of a ternary lipid mixture of lecithin, dicetyl phosphate, and a sterol, and (ii) an aqueous solution of a humectant such as glycerol, urea, sodium pyroglutamate, ornithine, or Spier-Pascher water solubles inside the liposome. The liposomes were described as a skin moisturizer. There is no disclosure of including a pharmaceutically active compound for transdermal delivery.

U.S. Patent No. 5,016,652 describes a patch for transdermal delivery of nicotine to reduce cigarette smoking. The patch optionally includes a skin penetration enhancer such as DMSO, sodium

lauryl sulfate, Azone, or a mixture of propylene glycol and oleic acid. The patent also references several other transdermal drug delivery patch patents.

In Willimann *et al.*, 1992, a composition comprising a "lecithin organogel" was described wherein small amounts of water were added to a solution of lecithin in an organic solvent to induce gelation. Transport rates of scopolamine and broxaterol across human skin samples in a Franz diffusion cell were reported to be about ten-fold higher in the lecithin organogel than in aqueous solution of these drugs at the same concentration. Transdermal passage of these compounds in the solution form of the mixture (*i.e.*, prior to addition of water to form a gel) were noted to be the same as when measured in the gel form. Successful transdermal delivery of amino acids and peptides was also noted. In that report, the ratio of water to lecithin was strongly emphasized as a critical feature. Thus, a parameter called $w_0 = [H_2O]/[lecithin]$ was described, and values of between 0-12 for this concentration ratio were described. The gelation was described entirely as a function of this parameter, and the incorporation of urea or a surfactant was neither disclosed nor suggested.

Veys, 1991, reviewed experience with ketoprofen which is a potent non-steroidal anti-inflammatory drug (NSAID). Topical delivery of the drug in the form of a ketoprofen gel was discussed and it was shown that absorption and elimination half-lives were 3.2 ± 2.4 hours and 27.7 ± 18.0 hours respectively.

Chi and Jun, 1990 & 1991, disclosed ketoprofen-pluronic F-127 formulations for topical delivery of ketoprofen.

In May 24-30, 1994, at the Jerusalem Conference on Pharmaceutical Sciences and Clinical Pharmacology, the state of the art in transdermal delivery of pharmaceutically active agents using liposomes was reviewed.

Tayar *et al.*, 1991, provide a study on the theoretical aspects of percutaneous penetration of drugs.

Seth, 1993, describes ibuprofen absorption from three different formulations.

Luisi *et al.*, 1990, provides a review of a new class of gels called lecithin gels. They note that gelation of lecithin (50-200 mM) in an organic solvent, occurs upon addition of between 1 to 12 moles of water per mole of lecithin, depending on which of the 50 different organic solvents tested is used to dissolve the lecithin. The physico-chemical properties of these organogels are discussed, and a model, which attempts to account for the peculiar viscosity characteristics of the gels, is proposed.

Schurtenberger *et al.*, 1990, and Scartazzini *et al.*, 1988, were authored by the same group as the above-discussed Luisi *et al.* review, which largely summarized the content of these papers.

Brief Summary of the Invention

This invention relates to a composition useful in the delivery of pharmaceutically active agents through the skin. The composition comprises a mixture of a polar lipid such as lecithin or phosphatidylcholine, a biocompatible organic solvent such as an isopropyl palmitate or isopropyl myristate ester, water, urea, and a biocompatible surfactant such as docusate sodium, docusate sodium

benzoate, or ibuprofen, at a pH of between about 6.0 and 8.0. In addition, the composition may optionally include cholesterol, or a preservative such as benzyl alcohol. Upon formulation of this composition with the pharmaceutically active agent, and, upon bringing the pH to the desired range, the formulation thickens and forms a gel for topical administration. In one embodiment of the invention, the composition is formulated with a non-steroidal anti-inflammatory agent, such as ibuprofen or ketoprofen. Such formulation is rapidly absorbed through the skin and provides local relief from pain. In another embodiment of the invention, the composition is formulated with an antineoplastic or other pharmaceutically-active agent. Such formulation is rapidly absorbed through the skin to provide local delivery to subcutaneous tumors and other subdermal sites in need of treatment. Several other formulations are also disclosed, such as those active as a muscle relaxant by virtue of an included active compound such as cyclobenzaprine.

Detailed Disclosure of the Invention

This invention relates to a composition useful in the delivery of pharmaceutically active agents through the skin. The composition comprises a mixture of a polar lipid such as lecithin or phosphatidylcholine, a biocompatible organic solvent such as isopropyl palmitate or isopropyl myristate esters, a surfactant, water, and urea, at a pH of between about 6.0 and 8.0 and preferably between 6.0 and 7.0. In addition, the composition may optionally include cholesterol or a preservative such as benzyl alcohol.

Preferably, the lecithin or phosphatidylcholine is of a high quality, pharmaceutical grade. Appropriate lecithin and phosphatidylcholine may be obtained as commercially available soya lecithin or soya phosphatidylcholine. Preferably, soya lecithin is used in the composition of this invention.

The biocompatible organic solvent may be any non-toxic solvent in which the polar lipid, the pharmaceutically active compound and urea are soluble, and which assists as a solubilizing vehicle for carrying pharmaceutically active compounds across the skin of a mammal. Acceptable esters for this purpose include, but are not limited to isopropyl esters. Preferably, the ester is isopropyl myristate or isopropyl palmitate, with isopropyl myristate being particularly preferred.

In preparing the composition of this invention, the polar lipid is dissolved in the organic solvent at mass ratios anywhere from 5:1 to 1:5. Preferably, the polar lipid and organic solvent are mixed in even mass ratios. Thus, in one embodiment of the invention, soya lecithin and isopropyl myristate are mixed in equal mass ratios and mixed until the lecithin is evenly distributed in the isopropyl myristate. This mixture, called lecithin organogel (L.O.), is stable and may be used even after prolonged storage without loss of activity.

Once the solvent-polar lipid mixture is thoroughly dispersed, the pharmaceutically active compound may be added and dissolved. This is most easily achieved by heating an aliquot of the solvent-polar lipid mixture and adding, on a mass basis, an amount of active compound equal to about 0.01 to 30% of the mass of the solvent-polar-lipid-and-mixing-until-completely-dissolved. Thus, for example, about 1-20 grams of ibuprofen (preferably the S-isomer) or ketoprofen in a powdered form

is added to about 100 grams of heated 1:1 soya lecithin:isopropyl myristate and allowed to dissolve with stirring. The pharmaceutically active compound may be an analgesic such as the non-steroidal anti-inflammatory agents ibuprofen and ketoprofen. It may be a topical anaesthetic such as lidocaine. It may be a steroid anti-inflammatory, such as cortisone. It may be an anti-neoplastic agent such as doxorubicin. It may be a peptide, protein, or hormone, such as platelet factor 4 which exhibits angiostatic activity. It may be a substance P antagonist such as capsaicin. It may be a muscle relaxant such as cyclobenzaprine. It may be an antifungal compound such as FLUCONAZOLE®. It may be an anti-inflammatory analgesic such as diclofenac sodium. It may be an anti-anginal compound such as nifedipine. In the event of using a proteinaceous pharmaceutically active compound, one must avoid adding the protein to a too-warm solution of solvent-polar lipid mixture as this might denature the protein if it is not thermostable.

Depending on the nature of the pharmaceutically active compound and the desired characteristics of the final formulation, a surfactant is included in the formulation at a concentration of between about 1-20% of the final composition mass. In the formulation including ibuprofen, we have found that ibuprofen exhibits surfactant properties, and addition of another surfactant is therefore not needed. In the case of ketoprofen, on the other hand, addition of a surfactant is beneficial. Preferably, the surfactant is one which is compatible with administration *in vivo* without elicitation of undesirable side effects. One such surfactant which has found wide-spread use in the formulation of stool softeners is docusate sodium and its more water soluble form, docusate sodium benzoate. Other appropriate ionic or non-ionic surfactants, such as polysorbate 80 or Tween 80, may naturally be used.

Either before or after addition of the pharmaceutically active compound, an amount of urea, preferably as an aqueous solution, is added to the solvent-polar lipid mixture. The urea is added so that the urea concentration will be between about 5% and 20% by mass of the final composition mass. Thus, using a 20% aqueous solution of urea, about 10 grams is added to about 100 grams of the solvent-polar lipid mixture with dissolved pharmaceutically active compound. In some instances, the pharmaceutically active agent will more readily dissolve if added after addition of the urea, and in other instances before the addition of urea. In any event, this is a choice easily made by those skilled in the art depending on the particular formulation being prepared and the solubility characteristics of the particular pharmaceutically active compound being solubilized. In the case of ibuprofen and a mixture of soya lecithin-isopropyl myristate, the ibuprofen is preferably added before addition of the urea. If the pharmaceutically active agent is a protein, it will be necessary to test the retention of biological activity of the protein upon exposure to the particular urea concentration used in this formulation as the chaotropic properties of urea are known to denature some proteins. Such a determination is easily conducted by one of ordinary skill in the art.

Upon formulation of the above described composition with the pharmaceutically active agent, the pH is adjusted to about a pH of 6.0 to 7.0. This is easily accomplished, for example, by addition of aqueous sodium hydroxide, as the compositions initially tend to have an acid pH. Naturally, if the

pharmaceutically active agent tends to produce very alkaline solutions, addition of acid to reduce the pH would be desirable. This is easily accomplished by addition of dilute citric acid or a biological buffer such as sodium carbonate or triethanolamine, as in tolamine salicylate. Once the composition reaches a pH in the range of about 6.0 to 7.0, the formulation thickens and forms a gel for topical administration.

In one embodiment of the invention, the composition is formulated with a non-steroidal anti-inflammatory agent, such as ibuprofen or ketoprofen. Such formulation is rapidly absorbed through the skin and provides local relief from pain. In another embodiment of the invention, the composition is formulated with an antineoplastic agent. Such formulation is rapidly absorbed through the skin to provide local delivery to subcutaneous tumors.

For ease of preparation, it is convenient to prepare a first gel composition, named speed-gel herein, which can be used to add to other components in the formulation of a final composition for topical administration. There are several possible formulations of the speed-gel. For example, a speed-gel may be prepared by mixing lecithin organogel (L.O.), as a 1:1 (m/m) mixture of lecithin and isopropyl myristate, with LID oil (a 1:1 [m/m] mixture of L.O. and docusate sodium), dissolving additional docusate sodium powder into this mixture, and then adding aqueous urea.

In one embodiment of the speed-gel formulation, the final concentrations are: L.O. = 25%; docusate sodium = 15%; urea = 10%; and water = 50%. These ratios may easily be varied such that the final amounts of each component are as follows: L.O. = 20-30%; docusate sodium = 10-20%; urea = 5-20%; and water = 30-60%. The speed-gel may then be added to solubilized active ingredients and other excipients which may be useful in solubilizing the active ingredient, such as DMSO, peppermint oil, glycerin, and/or polyethylene glycol. An homogenous mixture is then made by carefully blending the various components.

In experiments with the ingredients in the speed-gel, we tested whether a clear, amber colored, homogenous gel solution with reproducible and pleasant consistency could be made by altering the order and ratios of its constituents. Surprisingly, we found that all of the ingredients, namely lecithin organogel (L.O.), surfactant, aqueous urea, and a pH of between about 6.0 and 8.0, are necessary to achieve the desired gel. In addition, it is preferable that the components be compounded in the order: L.O., then surfactant, then aqueous urea, then pH adjustment. Addition of a lipophilic pharmaceutically active ingredient is preferably achieved by first solubilizing the active ingredient in the L.O. or by first solubilizing the ingredient in a minimal amount of DMSO or peppermint oil or like solvent, and then mixing it with the L.O. for compounding with the other components. Addition of an ionic or otherwise water-soluble active agent is achieved by either adding the agent to the L.O. or to the aqueous urea phase. Varying the approach to mixing the gel slightly but maintaining the integrity of the appropriate ratios of the components and the order of addition, still allows for the formation of an acceptable gel. Alteration of the ratios beyond the limits described herein, interferes with product consistency and gel formation. Thus, for example, when urea is eliminated from the formulation, a creamy colored and textured mixture is achieved which did not form a pleasant gel.

between pH 4.8 to pH 12.5. Likewise, when no surfactant is added, substituting an equal mass of L.O. in its place, a creamy and very viscous mixture was attained. Subsequent addition of docusate sodium did not rectify the unpleasant character of this mixture.

Once the formulations described above have been prepared, use of the formulations is a simple matter of applying the formulation to affected areas where transdermal delivery of the pharmaceutically active agent is desired. Thus, in the case of arthritis, formulations including ibuprofen are rubbed over the affected area such as the joints of the hands. Treatment repeated as pain symptoms reappear. In multiple applications of formulations prepared according to this invention prescribed by doctors around the country, doctors and patients have reported almost immediate reduction of arthritis associated pain.

In another aspect of this invention, a non-steroidal anti-inflammatory compound is formulated for delivery to hemorrhoidal tissue. As with treatments of arthritis associated pain, in multiple treatments, doctors and patients across the country have confirmed almost immediate reduction in hemorrhoidal associated pain. Thus, the gel of the instant invention is advantageously formulated in a suppository form or simply applied directly to the surface of affected tissues.

In other applications, such agents as anti-neoplastic drugs such as doxorubicin, or biologically active proteins, are formulated and directly applied to areas where local delivery of these active compounds is needed.

In another aspect of this invention, topical application of a hair growth enhancer is achieved by incorporation into the composition of an agent such as minoxidil. A concentration of about 0.1% to about 10%, and preferably about 2% minoxidil in the composition of this invention is desirable. In addition, a composition comprising an inhibitor of testosterone 5- α reductase, such as finasteride, could be used to advantage for this and other purposes. Finally, compositions comprising a mixture of minoxidil and a testosterone 5- α reductase inhibitor would be very beneficial for inducing increased hair growth. Because of the very good skin penetration achieved using the composition of this invention, lower doses of minoxidil could be delivered than are currently used in such formulations as ROGAINE®, which is 2% minoxidil in a solution of alcohol 60% v/v, propylene glycol and water.

In another aspect of this invention, a composition comprising an antibacterial agent is prepared, for example, by inclusion of bacitracin or another appropriate antibiotic. This allows for penetration of the antibacterial agent to sites of infection induced by puncture wounds.

In general, compositions of this invention are provided at a concentration of between about 0.1% to 20% by weight of active compound. In addition, compositions comprising more than one active ingredient are within the scope of this invention and could be administered to a recipient in need of more than a single active treatment at one localized spot. Thus, for example, a composition comprising an analgesic and an antifungal would both provide relief from acute pain and will provide long-term relief once the fungal infection has been completely eliminated.

It is contemplated that the compositions of this invention are applied topically as frequently as required as long as local reactions or toxicity due to the active ingredient do not become a problem. Thus, for example, a more rigorously monitored regimen of application may be required when an anti-neoplastic compound is being administered than when a readily metabolized non-toxic compound such as ketoprofen is administered. In the latter case, it would be acceptable for a person in need of such treatment to topically apply the composition as frequently as needed to achieve relief from local pain or inflammation.

While the foregoing description generally describes how to make and use the compositions and formulations of this invention, the following examples are provided to more specifically point out how to practice the invention. However, it should be clearly understood that the scope of this invention, as defined by the claims appended hereto, is not to be limited to the specifics of the following examples. Further, it should be understood that, in the specific compositions described and claimed, the percentages of active and other ingredients could be within at least a 10% different amount while still achieving an objective equivalent to the specifically disclosed compositions.

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Example 1 — Preparation of Speed-Gel

		<u>360 gm</u>
	LID Oil*	36 gm
20	Lecithin organogel** (L.O.)	72 gm
	Docusate sodium powder	36 gm
	Urea	36 gm
	Distilled water	180 ml

*LID oil is a 1:1 mixture of lecithin organogel:docusate sodium on a mass basis.

**L.O. is a 1:1 mixture of lecithin and isopropyl myristate.

25

1. The LID was added to L.O. and heated.
2. Docusate sodium powder was added, and the mixture was stirred until smooth.
3. Urea was added to water, heated, and added to step 2 with stirring.
4. pH was adjusted to between 6.5 to 6.9.

30

Speed-gel may just as easily be prepared as follows:

		<u>100 gm</u>
	L.O.	25 gm
	Docusate sodium benzoate powder	15 gm
	Urea	10 gm
	Distilled water	50 gm

35

The L.O. was heated and the docusate sodium benzoate powder was stirred into the heated L.O. until a smooth solution is prepared. The water was heated and the urea was dissolved into the

water, and the urea solution was then thoroughly mixed with the docusate sodium containing solution of L.O. The result was a consistent, transparent, amber colored gel with a pH of about 6.0.

Yet another way of making speed-gel is as follows:

	<u>100 gm</u>
5 L.O.	10 gm
LID	30 gm
Urea	10 gm
Distilled water	50 gm

10 The LID and L.O. were mixed well and a heated solution of water and the urea was prepared and added to the LID-L.O. solution. The result was a consistent, transparent, amber colored gel with a pH of about 6.0.

Example 2 — Preparation of Nifedipine Composition

	<u>#30 gm</u>
15 Nifedipine	0.3 gm
Dimethyl sulfoxide (DMSO)	43 drops
Polysorbate 80	2 ml
Speed-gel	qs to 30 gm

20

1. Nifedipine was dissolved in the DMSO with trituration in mortar.
2. 2 ml polysorbate 80 was added with trituration to thicken.
3. qs to 30 gm with new speed gel.

25 The composition was dispensed into a 1 oz. cc syringe with Luer tip cap and stored in a light-resistant bag.

Example 3 — Preparation of 5% Ketoprofen Composition

	<u>30 gm</u>
30 Ketoprofen	1.5 gm
Lecithin organogel	5 gm
Speed-gel	qs to 30 gm

35 The L.O. was heated and ketoprofen added and stirred until a consistent, fairly thin creamy-colored mixture was achieved. Speed-gel was then added, and the composition was treated to remove bubbles. The pH was adjusted to 6.8 with 30% NaOH. At about pH 6.0, the solution thickened, became clear, and from this point to pH 6.8, it was a thick, amber-colored, homogenous gel.

Example 4 — Preparation of Another 5% Ketoprofen Composition

	<u>30 gm</u>
Ketoprofen	1.5 gm
Tween 80	3.0 gm
5 Speed-gel	qs to 30 gm

Ketoprofen was added to Tween 80 and heated until a clear solution was achieved, then speed-gel was added.

10 Example 5 — Preparation of Another 5% Ketoprofen Composition

	<u>30 gm</u>
Ketoprofen	1.5 gm
Lecithin organogel	7 gm
Speed-gel	22 gm

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1. The ketoprofen was dissolved in lecithin organogel using moderate heat.
2. Speed-gel was added and the mixture was heated in a microwave to a clear thin gel.
3. The mixture was then set on a hot plate with stirring.
4. 30% NaOH was then added to bring the pH to 5.8-6.8 to form a gel.

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Example 6 — Preparation of 5% Ketoprofen, 2% Lidocaine Gel, Keto-Lido 5-2

	<u>30 gm</u>
Ketoprofen	1.5 gm
Lidocaine base	0.6 gm
25 Lecithin organogel	to wet
Speed-gel	qs to 30 gm

1. The ketoprofen and lidocaine were triturated to a fine powder.

2. The speed-gel was heated and added to the powders with stirring.

30 3. A few drops of lecithin organogel were added to the mixture to thicken.

4. The composition was dispensed into a jar for later use.

Example 7 — Preparation of a Ketoprofen (5%), Lidocaine (2%), Cyclobenzaprine (0.5%) Gel

	<u>60 gm</u>
35 Cyclobenzaprine	0.3 gm
Polysorbate 80	to wet
Keto-Lido-5-2 (from Example 6)	qs to 60 gm

10

1. The cyclobenzaprine was moistened with polysorbate.
2. The mixture was brought to final weight by trituration with Keto-Lido 5-2 compound of Example 6.

5 Example 8 — Preparation of Ketoprofen (5%), Lidocaine (2%), Cyclobenzaprine (0.5%) Gel

		<u>60 gm</u>
	Ketoprofen	3 gm
	Lidocaine base	1.2 gm
	Cyclobenzaprine	0.3 gm
10	L.O.	to wet
	Speed-gel	qs to 60 gm

1. The ketoprofen, lidocaine and cyclobenzaprine were triturated to a fine powder.
2. The speed-gel was heated and added to the powders with stirring.
3. A few drops of lecithin organogel were added to the mixture to thicken.
4. The formulation was dispensed into a jar for later use.

15 Example 9 — Ketoprofen 10% Gel

		<u>60 gm</u>
20	Ketoprofen	6 gm
	L.O.	7 gm
	Speed-gel	44 gm
	LID oil or polysorbate 80	2-3 ml to thicken

- 25 1. L.O. was added to the ketoprofen and stirred to a smooth paste.
2. Speed-gel was added and stirred to smooth paste and heated until clear.
3. 2-3 ml of LID oil was then added.
4. The pH and thickness were then adjusted by titrating the pH to 5.9-6.8 with 30% NaOH.

30 Example 10 — Ketoprofen 10%, Cyclobenzaprine 1% Gel

		<u>30 gm</u>
	Ketoprofen	3 gm
	Cyclobenzaprine	0.3 gm
35	Speed-gel	qs to 30 gm

1. The powders were triturated until fine.
2. The speed-gel was added and mixed until smooth.

Example 11 — 20% Ibuprofen Gel

A speed-gel containing ibuprofen was prepared without the need to add any additional surfactant because the ibuprofen itself acts as a surfactant. This formulation was prepared as follows:

	<u>100 gm</u>	
5	Ibuprofen	20 gm
	L.O.	25 gm
	Urea	10 gm
	Water	36 gm
	Benzyl Alcohol	1 ml
10	30% NaOH	5 ml

These reagents were mixed in the order listed above and brought to a pH of about 6.8. The gel has a pleasant amber color and light, even consistency.

15 Example 12 — Clinical Studies with the Gel of this Invention

In order to study the efficacy of the gel of this invention, a double-blind cross-over study is conducted wherein 10 volunteers suffering from arthritic conditions are provided with an NSAID containing gel formulation or, as a control, the gel absent the NSAID. In one particular study, the formulation of Example 11 is applied as the active treatment, and the gel in the absence of the ibuprofen, which is replaced with docusate sodium as the surfactant phase, is applied as the placebo. Neither the volunteers nor the physicians conducting the study are aware of the identity of the gel being administered. After a period of several days to several weeks, the experimental group is given the placebo, and the placebo recipients are crossed over to the active composition. In both the first and second phases of the study, objective criteria including swelling and joint tenderness, along with subjective criteria including general feelings of well-being, are scored for both the experimental group and the placebo recipients. In both phases, there is a statistically significant difference in both the objective and subjective scores for the experimental group, which scores showed that the composition containing ibuprofen provided significant relief while the placebo was much less efficacious in this regard. Topical administration of an aqueous solution of ibuprofen is also significantly less effective than ibuprofen applied in a speed-gel formulation.

Example 13 — Additional Clinical Studies

In a similar fashion to the study described in Example 12, studies are conducted to measure the muscle spasm reducing effects of cyclobenzaprine, the tumor treatment efficacy of compositions containing anti-tumor compounds such as doxorubicin, and any number of other agents the efficacy of which is desirable in a transdermal formulation. In each case, results with the experimental composition as opposed to the placebo are significantly better.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

References CitedU.S. Patents

5,093,133

5,210,099

3,154,470

4,385,049

4,794,106

5,016,652

Other References

Chi, S.C., H. W. Jun (1990) *J. Pharmaceutical Sci.* 79:974-977.

Chi, S.C., H. W. Jun (1991) *J. Pharmaceutical Sci.* 80:280-283.

Luisi *et al.* (1990) *Colloid Polym. Sci.* 268:356-374.

May 24-30, 1994, at the Jerusalem Conference on Pharmaceutical Sciences and Clinical Pharmacology (see *J. Pharmaceutical Sciences* 83:1189-1203, September 1994).

Schurtenberger *et al.* (1990) *J. Phys. Chem.* 94:3695-3701.

Scartazzini *et al.* (1988) *J. Phys. Chem.* 92:829-833.

Seth, P. L. (1993) *Arzneim-Forsch/Drug Res.* 43(11):919-921.

Tayar *et al.* (1991) *J. Pharm. Sci.* 80:744-749.

Veys, E. M. (1991) *Scand. J. Rheumatol. Suppl.* 90:3-44.

Willimann, H. *et al.* (1992) *J. Pharmaceutical Sci.* 81:871-874.

Claims

- 1 1. A composition for the delivery of a pharmaceutically active substance through the skin
2 of a mammal which comprises a biocompatible organic solvent, a polar lipid, a surfactant, water,
3 urea and the pharmaceutically active substance to be delivered, at a pH of about 6.0 to 8.0.

- 1 2. The composition, according to claim 1, wherein the biocompatible organic solvent is
2 an isopropyl ester.

- 1 3. The composition, according to claim 2, wherein the isopropyl ester is isopropyl
2 myristate or isopropyl palmitate.

- 1 4. The composition, according to claim 1, wherein the polar lipid is lecithin or
2 phosphatidylcholine.

- 1 5. The composition, according to claim 4, wherein the ester is isopropyl myristate.

- 1 6. The composition, according to claim 5, wherein the urea is present at a concentration
2 of about 5 to 20% by mass of the final composition.

- 1 7. The composition, according to claim 6, wherein the polar lipid is lecithin.

- 1 8. The composition, according to claim 7, wherein the surfactant is selected from the
2 group consisting of docusate sodium, docusate sodium benzoate, docusate calcium, and ibuprofen.

- 1 9. The composition, according to claim 1, wherein the pharmaceutically active substance
2 is an analgesic, an anti-inflammatory, a biologically active protein or an antineoplastic compound.

- 1 10. The composition, according to claim 6, wherein the pharmaceutically active substance
2 is an analgesic, an anti-inflammatory, a biologically active protein or an antineoplastic compound.

- 1 11. The composition, according to claim 10, wherein the pharmaceutically active
2 substance is a non-steroidal anti-inflammatory agent.

- 1 12. The composition, according to claim 11, wherein the pharmaceutically active
2 substance is ibuprofen or ketoprofen.

1 13. A composition comprising, as a percentage of the mass of the final composition:

2 (a) Lecithin 10-30%;
3 (b) isopropyl myristate 10-30%;
4 (c) urea 5-20%;
5 (d) water 30-60%;
6 (e) a surfactant 10-20%.

1 14. The composition, according to claim 13, further comprising about 1% nifedipine.

1 15. The composition, according to claim 13, further comprising about 5-10% ketoprofen,
2 or 5-20% ibuprofen.

1 16. The composition, according to claim 15, further comprising about 2% lidocaine.

1 17. The composition, according to claim 16, further comprising about 1%
2 cyclobenzaprine.

1 18. A method of making a composition for transcutaneous delivery of a pharmaceutically
2 active substance which comprises:

3 (a) dissolving a polar lipid in an about equal mass of biocompatible organic solvent;
4 (b) adding a surfactant to the composition of step (a) to a concentration of about
5 10% to about 20%;
6 (c) dissolving a pharmaceutically active compound in the solvent-polar lipid,
7 surfactant mixture of step (b) to a concentration of about 0.01% to about 30%;
8 (d) adding aqueous urea to a concentration of about 5% to about 20%; and
9 (e) adjusting the pH to between about 6.0 to 8.0.

1 19. A method of treating a localized medical condition in a mammal which comprises
2 administering a pharmaceutically active agent known to be beneficial in the treatment of such
3 condition by delivering across the skin of the mammal a pharmaceutically effective amount of said
4 pharmaceutically active agent by topical application of a composition comprising said
5 pharmaceutically active agent wherein said composition further comprises:

6 soya lecithin;
7 isopropyl myristate;
8 urea; and
9 optionally comprising docusate sodium;

10 wherein the final formulation has a pH in the range of about 6.0 to 7.0.

1 20. The method, according to claim 19, wherein said localized medical condition is
2 selected from the group consisting of: arthritis; bunions; hemorrhoids; subcutaneous or cutaneous
3 cancer; hair loss; cutaneous or subcutaneous bacterial infection; and fungal infections.

1 21. The method, according to claim 20, wherein the pharmaceutically active agent is
2 selected from the group consisting of: a non-steroidal anti-inflammatory; a steroid anti-
3 inflammatory; an anti-neoplastic agent; a hormone; a biologically active protein; a substance P
4 antagonist; an antifungal; an anaesthetic; and anti-anginal; a muscle relaxant; minoxidil; and a
5 testosterone 5- α reductase inhibitor.

1 22. A composition prepared according to the method of claim 18.

1 23. A composition consisting essentially of:

2 lecithin 10-15%;
3 isopropyl myristate 10-15%;
4 docusate sodium 10-20%;
5 urea 5-15%; and
6 water 25-60%;

7 and a pharmaceutically active ingredient present at between 0.1-40%, at a pH of between about
8 6.0 to 7.0.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/03730

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/06 A61K47/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,40 21 082 (LAUTENSCHLÄGER) 23 January 1992 see the whole document see page 4, line 14 see page 5, line 32 see page 9; example 5 see page 10; example 7 ---	1-13, 18-21
X	DATABASE WPI Week 8652 Derwent Publications Ltd., London, GB; AN 86-344274 XP002008865 & JP,A,61 260 015 (TAISHO PHARMACEUT KK) , 18 November 1986 see abstract ---	1,4,6,7, 9-11, 18-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search 19 July 1996	Date of mailing of the international search report 29. 07. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Benz, K

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/03730

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Week 8945 Derwent Publications Ltd., London, GB; AN 89-327620 XP002008866 & JP,A,01 242 521 (NIKKO CHEMICALS KK), 27 September 1989 see abstract ----- W0,A,89 00077 (LUISI) 12 January 1989 see page 15 - page 16; example 5 ----- FR,A,2 288 515 (GRADSTEIN) 21 May 1976 see page 3; example 1 -----	1-22
A		1-22
A		8,22

1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/03730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/03730

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
DE-A-4021082	23-01-92	NONE			
WO-A-8900077	12-01-89	CH-A- 681427	31-03-93	DE-D- 3887309	03-03-94
		EP-A- 0323494	12-07-89		
FR-A-2288515	21-05-76	NONE			